

WHAT IS CLAIMED IS:

1. A method of screening a population of nucleic acids for a novel sequence, the method comprising:

providing a population of nucleic acid sequences;

partitioning said population into one or more subpopulations of nucleic acids;

identifying a first nucleic acid sequence in the subpopulation of nucleic acid sequences;

and

comparing the first nucleic acid sequence to a reference nucleic acid sequence or sequences, wherein the absence of the first nucleic acid sequence in the reference nucleic acid or nucleic acid sequences indicates the first nucleic acid is a novel nucleic acid sequence.

2. The method of claim 1, wherein said DNA population is a cDNA population derived from a population of RNA molecules.

3. The method of claim 2, further comprising partitioning the RNA molecules.

4. The method of claim 2, wherein said cDNA population is derived from the 5' ends of the RNA molecules.

5. The method of claim 2, wherein said cDNA population is derived from the interior regions of the RNA molecules.

6. The method of claim 2, wherein said cDNA population is derived from the 3' ends of the DNA molecules.

7. The method of claim 2, wherein said partitioning step comprises hybridization of a probe nucleic acid sequence to the population of nucleic acids.

8. The method of claim 2, wherein said ~~partitioning~~ step comprises digesting the cDNA molecules with one or more restriction enzymes.

Sub C3
9. The method of claim 8, further comprising ligating adapter oligonucleotides to the termini of the digested cDNA molecules, ¹ ~~thereby producing ligation products.~~

10. The method of claim 9, further comprising amplifying the ligation products.

Sub C4
11. The method of claim 10, further comprising separating the amplified products.

12. The method of claim 11, wherein said separating is by gel electrophoresis.

Sub C5
13. The method of claim 11, wherein the first nucleic acid sequence is identified by comparing the size of one or more digestion products produced by a member of the subpopulation of nucleic acids to the sizes of fragments generated by the same restriction enzyme or enzymes in said reference nucleic acid or nucleic acids.

14. The method of claim 11, further comprising
recovering one or more size-separated digestion products;
reamplifying the recovered products; and
separating the reamplified products.

Sub C6
15. The method of claim 14, wherein said separating is by gel electrophoresis.

16. The method of claim 15, wherein the first nucleic acid sequence is identified by comparing the size of one or more digestion products produced by a member of the subpopulation of nucleic acids to the sizes of fragments generated by the same restriction enzyme or enzymes in said reference nucleic acid or nucleic acids.

17. The method of claim 9, further comprising:
 inserting the ligated adapter oligonucleotide into a cloning vector to form a vector-insert;
 transforming the vector-insert into a suitable host;
 culturing transformed host under conditions allowing for replication of the vector-insert;
 recovering the vector-insert from said host; and
 digesting the vector-insert with one or more restriction enzymes, thereby releasing said
 insert; and
 comparing the size of the insert to sizes of fragments generated by the same restriction
 enzyme or enzymes in said reference nucleic acid or nucleic acids.

18. The method of claim 1, wherein comparing is by determining at least a portion of the
 nucleotide sequence of the first nucleic acid sequence and comparing the nucleotide sequence to
 the nucleotide sequence of one or more reference nucleic acids.

19. The method of claim 1, wherein comparing is by hybridizing the first nucleic acid
 sequence to one or more of the reference nucleic acid sequences.

20. A method for equalizing the representation of nucleic acids in a population of nucleic
 acids, the method comprising:

providing a population of nucleic acid sequences, wherein said population comprises a
 first nucleic acid and a second nucleic acid having a nucleic acid sequence distinct from the first
 nucleic acid, and wherein said first nucleic acid is present at a higher level in said population
 than said second population;

partitioning said population into one or more subpopulations of nucleic acids; and

comparing the levels of said first nucleic acid sequence to the levels of said second
 nucleic acid sequence in the subpopulation of nucleic acid sequences, wherein a lower level of
 the first nucleic acid sequence relative to the second nucleic acid sequence indicates the
 representation of said first and second nucleic acid sequences are normalized.

21. A method for producing a population of nucleic acid molecules enriched for 5' regions of mRNA molecules, the method comprising:

providing a population of RNA molecules, said population including RNA molecules having a 5' terminal Gppp cap structure and a 5' terminal phosphate group;

contacting said population of RNA molecules with a phosphatase under conditions that result in removal of the 5' terminal phosphate group while leaving the 5' terminal Gppp cap structure intact;

inactivating said phosphatase;

contacting the population of RNA molecules with a pyrophosphatase under conditions that result in the removal of the 5' terminal Gppp and the formation of a 5' phosphate group;

annealing an oligonucleotide in the presence of an RNA ligase to form a hybrid molecule; and

forming a cDNA from said oligonucleotide.

22. A method of identifying an RNA sequence in a sample comprising a plurality of RNA sequences, the method comprising:

synthesizing cDNA copies of a plurality of RNA species to form a cDNA sample;

determining the size of one or more of said cDNA molecules in said cDNA sample;

comparing the size of said sample with the size of a reference nucleic acid; and

thereby identifying the cDNA sequence

23. The method of claim 22, wherein said cDNA molecules are digested with one or more restriction enzymes prior to the determining step.

24. The method of claim 23, further comprising ligating adapter oligonucleotides to the termini of the digested cDNA molecules prior to the determining step.

25. The method of claim 22, wherein said identifying step comprises comparing the size of one or more digestion products produced by one or more said cDNA molecules to a reference nucleic acid or nucleic acids.

26. A method of identifying an RNA sequence in a population of RNA sequences, the method comprising:

- (a) removing 5' terminal pppG from RNAs in said population to form a population of RNAs having terminal 5' phosphate groups;
- (b) ligating a linker oligonucleotide to the terminal 5' phosphate groups of RNA molecules in said population of RNAs;
- (c) synthesizing complementary cDNA molecules from said population of RNA molecules to form a cDNA sample;
- (d) digesting said complementary cDNA molecules with at least one restriction enzyme;
- (e) ligating an adapter molecule to the digested cDNA molecules;
- (f) amplifying the molecules produced in step (e);
- (g) identifying the amplified molecules of step (f); and
- (h) comparing the amplified molecules to one or more reference nucleic acids.

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